ORAL DELIVERY OF NUCLEIC ACID VACCINES BY PARTICULATE COMPLEXES

RELATED APPLICATION

This application claims the benefit of Provisional Application Ser. No. 60/071,679, filed Jan. 16, 1998.

TECHNICAL FIELD OF THE INVENTION

This invention is related to the field of immunology and allergic diseases. In particular it relates to the area of food allergies.

BACKGROUND OF THE INVENTION

IgE is critical in the pathogenesis of various allergic diseases, including type I immediate hypersensitivity (1), and the best-characterized food-allergic responses involve IgE-mediated responses (2). A failure to develop, or a breakdown in, oral tolerance results in the production of food-specific IgE Abs. IgE Abs and allergens activate mast cells and basophils through the high affinity IgE receptor (Fce RI), and systemic anaphylactic reaction are provoked by histamine and other mediators released from activated mast cells and basophils (3). Numerous clinical and experimental animal studies have indicated the pivotal role of T cells and cytokines in the development of IgE-associated allergic diseases (4–5). In particular, a subset (Th2) of T cells, which has been distinguished functionally by its pattern of cytokine secretion, is thought to play a key role. Th2 cells are thought to promote allergic responses through their secretion of the cytokines,IL-4 and IL5, which promote IgE production and mast cell development, and eosinophilia, respectively. Cytokines released by the opposing pathway (Th1), such as IFN-γ, inhibit the development and expansion of Th2 cells and cytokine production. These studies demonstrate the importance of cytokines in the regulation of Th2 responses, and suggest potential therapeutic approaches to modify the development of IgE- and Th2-associated phenotypes.

Food allergy (including allergic reactions to nuts, egg, milk, and seafood) is a major health problem because of the potential severity of allergic reactions, the nature of the allergic hypersensitivity, and the ubiquitous use of food products. Recent surveys in the US determined that food allergies are the most common single cause of anaphylaxis treated in hospital emergency departments (6, 7). In both reports, food-induced anaphylaxis accounted for about one-third of anaphylactic cases, with peanuts and tree nuts accounting for the majority of reactions to foods. It is believed that about 100 fatal cases of food-induced anaphylaxis occur in the US each year (8), that peanuts are one of the leading causes of food-allergic reactions (9, 10), and that peanuts and tree nuts together represent the leading cause of fatal and near-fatal food-induced anaphylaxis (6, 8, 11–12).

While food allergy has become recognized as an increasing national health problem, the only proven treatment of food allergy consists of educating the patient in the complete avoidance of all possible sources of food allergens. However, frequent accidental ingestions [up to 50% of peanut allergic patients per year (13–14)] occur due to the ubiquitous use of peanut protein in a variety of food products. Two small trials with standard rush immunotherapy for peanut allergy demonstrated limited efficacy and unacceptable side effects (15). Given the large number of patients with potentially fatal food allergy, the extreme difficulty in avoiding all food allergen exposure, and the lack of efficacy for standard immunotherapy, novel and effective therapeutic strategies are urgently needed.

Utilizing a combination of oral and intraperitoneal (i.p.) sensitizations, we have recently shown that C3H mice develop peanut-specific IgE Abs and experience systemic anaphylaxis upon challenge with peanut proteins (16). We demonstrated that mice sensitized orally with peanut proteins (PN) followed by i.p. challenge with PN exhibit similar features observed in allergic patients, including active systemic anaphylaxis such as itching and pilar erecti; and with sensitization using combined oral feeding and i.p. injection with adjuvants [cholera toxin (CTx) and alum, respectively], the more severe symptoms including death were induced. Several parameters of the hypersensitivity response in mice can be monitored, including symptom scores, levels of serum specific IgE, and challenge-induced changes in plasma histamine, mast cell degranulation and vascular leakage. As a corollary, Snider et al. (17) demonstrated that oral sensitization of mice followed by i.p. challenge with hen egg lysozyme or OVA in the presence of CTx results in fatal systemic anaphylaxis in 80% of sensitized mice. The fatality was associated with elevated levels of plasma histamine and degranulated mast cells in a number of target organs. The finding that a more severe anaphylactic reaction is seen in mice sensitized and challenged with Ag and CTx as an adjuvant is consistent with recent studies demonstrating that CTx can promote Th2-type responses (18–19). These studies further suggest an important role for Ag-induced IgE and Th2 responses in the development of hypersensitivity, and provide a useful model to examine the regulatory mechanisms of peanut-induced hypersensitivity, and to explore the utility of the DNA-based immunization approach.

Recent advances in the manipulation of the immune system utilizing "DNA-based immunization" has provided an important and novel therapeutic approach in a variety of human diseases (20). DNA-based immunization has been used to generate and/or modify the host immune response, with the ultimate purpose of preventing, reversing, stabilizing, or slowing down the progression of disorders. This approach in manipulating the immune system has generated great interest by investigators searching for novel approaches to protect the host against various diseases (21–24). Injection of "naked" plasmid DNA (PDNA) encoding Ag results in long-lasting cellular and humoral immune responses to Ag (25). Successful immunization has been demonstrated with administration of pDNA by intramuscular, intradermal, intravenous, and subcutaneous routes (20, 26–28). It has been reproducibly demonstrated that intramuscular injection of pDNA provoke long-term immune responses characterized by the synthesis of specific IgG Abs, and by the efficient generation of CD8+cytotoxic T cells and CD4+Th1 cells (29). Recent results have also indicated that the pDNA persists episomally without replication or incorporation into the host cell genome (20). These new and exciting developments thus show promise of safe and effective therapy for various diseases.

Using intramuscular gene delivery, Hsu et al (30–31) have recently demonstrated that intramuscular injection of rats and mice with a pDNA encoding a house dust mite allergen (Der p 5) prevent the induction of IgE synthesis, histamine release, and airway hyper responsiveness in animals challenged with aerosolized allergen. Raz et al. (32) showed that β-galactosidase (β-gal)/alum-primed Balb/c mice immunized intradermally with pDNA encoding β-gal show a 66–75% reduction in the level of β-gal-specific IgE in 6 weeks. Also this pDNA immunization protocol induced